Clinical Impacts of Histological Subtyping Primary Breast Cancer

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Abstract. *Background: Treatment decisions in breast cancer depend on TNM classification and the assessment of additional variables with have an impact on survival. We examined whether histological subtyping breast cancer as either ductal or lobular is related to disease outcome. Patients and Methods: We examined a large data base of 14198 breast cancer patients. Results: Histological sub-classification of invasive breast cancer as either ductal or lobular is not correlated with disease outcome. However, the data further showed that invasive lobular carcinomas have a higher probability of being oestrogen receptor (ER)- and progesterone receptor (PR)-positive and a lower probability of being c-erbB2-positive. They also showed a higher average age at the time of diagnosis in comparison with invasive ductal carcinoma. Local recurrence rates were lower in invasive lobular carcinoma in comparison with invasive ductal carcinoma (3.5% vs. 6.2%; p=0.031). The multivariable Cox regression analysis showed that ER, PR, nodal status, grade and tumour size predicted disease outcome with statistical significance, while the histological subtype (invasive ductal or lobular) was not a significant predictor of disease outcome. Conclusion: Histological sub-classification of invasive breast cancer as either ductal or lobular is not correlated with disease outcome. On the other hand our data gives some indication that lobular and ductal breast cancer appear to be different biological entities.*

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Breast cancer can be classified by a set of clinical and morphological criteria in order to provide a basis for far-reaching clinical decisions concerning surgery, treatment with cytostatic and/or anti-hormonal medications, the application of radiation, or indeed whether to recommend any medical treatment at all. The pathological report based on macroscopic and microscopic evaluation results in a morphological diagnosis of individual tumour specimens consisting of eight to eleven variables such as: primary tumour size (T), nodal status (N), distant metastasis (M), tumour grading (G), stage, oestrogen receptor status (ER), progesterone receptor status (PR), human epidermal growth factor receptor 2 (c-erbB2), lymphatic invasion (L), vascular invasion (V) and residual tumour (R). An additional criterion is the histological subtype (1, 2), which can be invasive ductal, invasive lobular or specified (such as colloid or tubular carcinoma). There are up to 30 specified subtypes following the classification of the World Health Organization (WHO), some of them poorly defined (3). The present study was based on a large number of breast cancer patients. The following three hypotheses were tested: (i) invasive lobular and ductal carcinomas have different survival rates, (ii) invasive lobular carcinoma and invasive breast cancer differ in respect to the aforementioned WHO descriptors of invasive breast cancer, and (iii) local recurrence is more frequently observed in invasive lobular carcinoma than in invasive ductal carcinoma.

Patients and Methods

Patients. Three independent groups of breast cancer patients from different sources were investigated in order to avoid any study bias due to patient, family, or doctor preferences for local clinics. However, all patients belonged to a South German population in a city of 500,000 inhabitants and its suburbs (Stuttgart).

Group A: A group of patients with primary breast carcinoma from 1984 to 2006 was investigated (N=2616). After 1995, a

complete assessment of all patients suffering from primary breast cancer in the Robert Bosch Hospital was performed. Data concerning recurrence (local, distant or one of both) and c-erbB2 status were available only for this group. Treatment modalities were available for this group and were classified in three subgroups: (i) tamoxifen treatment (N=988), (ii) chemotherapy with anthracycline-containing regimen (N=559), and (iii) patients treated with CMF chemotherapy (N=237). For all three subgroups, the study examined whether the histological type had an influence on disease outcome given a treatment with the described regimen had taken place.

Group B: All patients suffering from primary breast cancer after 1995 were assessed in a district hospital (N=470). Data on patients were collected and updated by interviews with family doctors.

Group C: All patients registered the Onkologischer Schwerpunkt Stuttgart (OSP) (4) were included except those treated in the Robert Bosch Hospital (N=11,112).

Data on all three populations (N=14,198) were merged. The following clinical and pathological data were analysed for each patient: (i) a complete report with the histological diagnosis and TNM classification, (ii) survival data from OSP including information of the resident's registration office, (iii) the steroid receptor status (ER, PR), (iv) the c-erbB2 status for the cases of group A, and (v) reports about medical treatment for group A patients.

For most data categories, data on fewer than 10% of the patients were missing besides c-erbB2, L,V and R, from which c-erbB2 was available only for group A patients (N=1,591 patients). For ER, the rate of missing data was 11.31%, 11.64% for PR, and 57.3% for menopausal status.

Pathological reports. For each case, tumour size (T1-T4), nodal status (N0-3), assessment of metastasis (M0-M1) and grading (G1-G3) were obtained from the files of the department of surgical pathology of the relevant hospital, following WHO recommendations (1, 2). The pathological reports were carried out in five different Departments of Pathology. The exact number of pathologists responsible for diagnoses was unknown, however, it was more than 20. A study by Sloane *et al*. (3) confirmed the robustness of breast cancer classification.

Biological parameters of primary breast cancer. ER and PR were assessed by immunohistochemical methods. The results were measured in a score ranging from 0 to 12. The ER and PR scores were assessed by multiplying the frequency of nuclear staining in tumour cells by the four-scale intensity of immunohistochemical staining (0: absent, 1: low, 2: moderate and 3: strong) following the recommendations of Remmele and Stegner (5). The staining frequency was rated according to the percentages of immunostained tumour cells as follows: 0=no stained tumour cells, 1: 1-10%, 2: 11-50%, 3: 51-80% and 4: 81-100%. The following scores were possible: 0, 1, 2, 3, 4, 6, 8, 9 and 12. Based on a recommendation from OSP, values of 0 and 1 were classified as ER- or PR-negative and values ≥2 as positive. ER and PR reporting was similar at all Departments of Pathology contributing to the study.

The cerbB-2 status was assessed by either CB-1 immunohistochemical staining or the Herceptin test (Dako, Germany). It was given a four-scale score as follows: 0: absence of membrane staining, 1: weak and incomplete membrane staining for c-erbB2 in <10% of all tumour cells, 2: weak or moderate membrane staining in >10% of all tumour cells and 3: strong membrane immunohistochemical staining in >10% of the tumour cells. Score 3 was classified as positive, with scores 0-2 being classified as negative for c-erbB2.

Statistical methods. All data were analysed by several software systems including a recently developed software package by Klenk and co-workers (6, 7). OSP data were collected by the Kratzur system (4, 8) which is based on the Cache database (4). The patient's status (alive or dead, cause of death) was interrogated each year at their registration office. All data was transferred *via* Microsoft Excel (Windows Corp., Redmont, WA, USA). Odds ratio (OR), as well as survival data, were calculated by the R-package (9), available from http://www.r-project.org, together with the epitools and survival R-packages, available from http://cran.r-project.org/web/packages.

The following statistical tests were applied: Wilcoxon or Kruskal Wallis test for ordered data, chi-square test for categorical data, log-rank test to compare the survival of several groups, and Cox regression for multivariable survival analysis. *P*-values were considered to be significant when $p<0.05$ and highly significant when $p<0.001$. Overall survival (OS) was defined as the time from diagnosis (nearly identical with the date of surgical intervention) to any death, either from tumour or from an unknown cause.

Results

Patient characteristics (Table I). The clinical and pathological reports of 14,198 patients were analysed. The average follow-up time was 5.86 years (median 5.03, range: 0.1-23.07 years). The average follow-up time of the three different groups ranged from 5.08 to 5.99 years (standard deviation range: 3.32-4.43 years) ($p<0.001$). Differences in the survival data between the three patient groups was not significant ($p=0.37$). Group B patients tended to be older and more often M1 (12.6% *vs*. 6.2% (group A) and 5.1% (group C)), pN3 (2.6% *vs*. 2.3% and 1.4%), ER-positive (81.8% *vs*. 77.6% and 68.9%) and PR-positive (73.5% *vs*. 70.2% and 56.5%).

Histological types of breast cancer (Table II). Survival for primary invasive breast cancer showed no significant differences between primary invasive breast cancer, classified as invasive lobular, ductal or specified ($p=0.145$). This was also true when the specified forms were excluded ($p=0.745$). The 1-, 3-, 5-, 10- and 15-year survival rates are reported in Table II. Median survival time was 14.7 years (95% confidence interval (CI): 13.9-15.5 years) for invasive ductal carcinoma and 13.5 years (95% CI: 12.5-15.1 years) for invasive lobular carcinoma. The difference between the survival rates was less than 2% for all time periods except for the 15-year survival. However, histological typing of invasive breast cancer as either lobular or ductal was related to pN (lobular carcinoma: 60.5% in pN0, 30.6% in pN1, 8.9% in pN2 or pN3, $p=0.0002$; ductal carcinoma: 56.4% in N0, 35.6% in N1, 7.9% in N2 or N3), T (lobular carcinoma: 40.2% in pT1, 42.0% in pT2, 10.1% in pT3 and 7.7% in

Table I. *Study patient characteristics (N=14,198).*

Variable	Value	%	Log-rank test	*p*-Value
Age (years)				
Average	59.7		1635.0	10^{-15}
Median	59			
SD	13.3			
Range	18-101			
Menopausal status				
Pre-	1,610	26.6	30.7	4×10^{-6}
Peri	197	3.2		
Post-	4,256	70.2		
Missing values	8,135			
Stage				
I	4,502	35.7	2411.0	10^{-15}
II	5,921	47.0		
III	1,594	12.7		
IV	585	4.6		
Missing values	1,596			
pT				
T1	6,545	46.1	1466.0	10^{-15}
T2	5,712	40.2		
T3	854	6.0		
T4	1,087	7.7		
Missing values	0-			
N				
N0	7,902	57.9	1503.0	10^{-15}
N1	4,645	34.1		
N2	867	6.4		
N3	220	1.6		
Missing values	564			
M				
M0	12,211	94.5	2097.0	10^{-15}
M1	718	5.5		
Missing values	1,269			
Grading				
G1	1,403	10.3	352.0	10^{-15}
G2	8,895	65.3		
G3	3,318	24.4		
missing values	582			
ER				
Negative	3,640	28.9	48.3	10^{-12}
Positive	8,952	71.1		
Missing values	1,606			
PR				
Negative	5,030	40.1	102.0	10^{-15}
Positive	7,515	59.9		
Missing values	1,653			
c-erbB2[a]				
Negative (score 0-2)	1,386	87.1	11.6	0.003
Positive (score 3)	205	12.9		
Missing values	1,015			

[a]Only group A data; SD, standard deviation.

Table II. *Histological subtypes of primary breast cancer (p=0.145).*

Time	Histological subtype					
	Invasive ductal			Invasive lobular		
	Survival (OS) (%)	95% Confidence interval	Patients at risk	Survival (OS) (%)	95% Confidence interval	Patients at risk
1-Year	97.2	96.9-97.5	9654	97.7	97.0-98.5	1523
3-Year	83.7	82.9-84.4	6376	85.0	83.0-86.9	989
5-Year	75.4	74.5-76.3	4713	76.7	74.3-79.1	674
10-Year	59.8	58.5-61.1	1636	59.6	56.2-63.3	208
15-Year	47.3	45.3-49.3	286	43.4	37.8-49.9	38

pT4; ductal carcinoma: 46.5% in pT1 , 40.4% in pT2, 5.4% in pT3 and 7.7% in pT4, $p<0.0001$), grading (lobular carcinoma: 2.6% in G1, 80.0% in G2 and 18.4 in G3; ductal carcinoma: 9.8% in G1, 64.8 in G2 and 25.4 in G3, $p<0.0001$) or the menopausal status (lobular carcinoma: 20.5% in premenopausal patients, 3.0% in perimenopausal patients and 76.5% in postmenopausal patients; ductal carcinoma: 27.5% in premenopasual patients, 3.4% in perimenopausal patients and 69.1% in postmenopausal patients, $p=0.0004$). There was no correlation between M and the histological subtype (OR=1.16, 95% CI: 0.930-1.450; $p=0.20$). OR for a c-erbB2 score 3 was 1.57 (95% CI: 1.27-1.95; $p<0.001$) in invasive ductal carcinoma. Therefore, compared to ductal carcinoma, invasive lobular carcinoma was found significantly more frequently in postmenopausal women (76.5% *vs*. 69.0%) or pN0 cases (60.5% *vs*. 56.4%) and less frequently in T1 tumours (40.2% *vs*. 46.5%; $p<0.0001$).

Excluding pT4 and M1 cases of breast cancer from the analysis did not alter the negative input of the histological type on disease survival (chi square=0.3, $p=0.564$). Also the grade did not influence the lacking clinical impact of the histological subtype (only G1 cases, $p=0.983$; only G2 cases, $p=0.351$; only G3 cases, $p=0.14$)

When the influence of treatment groups (only available in group A) was examined, there were enough patients for analysis in three treatment groups: (i) tamoxifen-treated patients, (ii) patients under CMF chemotherapy, and (iii) anthracycline-containing regimens. In all three groups, the histological type as either ductal or lobular had no effect on disease outcome ($p=0.49$ in the tamoxifen group, $p=0.49$ in the CMF group and $p=0.51$ in the anthracycline group).

Biological disease modifier and histological subtypes (Table III). The results demonstrated that histological subtypes are clearly correlated with the receptor steroid expression. ER/PR negativity was clearly related to the invasive ductal carcinoma and ER/PR positivity to the invasive lobular subtype, giving an OR of 1.775 (95% CI: 1.556-2.024; $p<0.0001$) for ER (lobular carcinoma 80.5% ER-positive *vs*. ductal carcinoma 70.0% ER-positive) and an OR of 1.713

Table III. *Correlation of histological subtype and receptor expression.*

Steroid receptor expression	Histological subtype			
	Invasive ductal		Invasive lobular	
	N	%	N	%
ER^-/PR^-	2,313	24.1	202	12.9
ER^+/PR^-	1663	17.3	257	16.4
ER^-/PR^+	569	5.9	105	6.7
ER^+/PR^+	5,070	52.7	1,001	64.0

Table IV. *Recurrence and histological subtype (data only available for group A patients*).*

	Histological subtype			
	Invasive ductal N	%	Invasive lobular N	%
Local recurrence				
No	1,725	93.9	470	96.5
Yes	113	6.1	17	3.5
Chi-square=4.66; p=0.031				
Distant metastasis				
No	1,519	82.7	419	86.2
Yes	319	17.3	67	13.8
Chi-square=3.28; p=0.070				

*In 137 cases, the clinical reports reported a recurrence, but without mentioning whether local or distant.

(95% CI: 1.525-1.923; p<0.0001) for PR (lobular carcinoma 70.8% PR-positive *vs*. ductal carcinoma 58.6% PR-positive). C-erbB2 data were available only for group A.

With regard to the steroid receptor expression and its relation to the c-erbB2 score, a different situation was observed in invasive ductal and lobular carcinoma. A significant inverse relationship was found between expression of either ER and c-erbB2 (OR=0.38, 95% CI: 0.27-0.54) or PR and c-erbB2 (OR=0.36, 95% CI: 0.26-0.51) in invasive ductal carcinoma: 8.8% of ER-positive breast tumours were c-erbB2-positive as compared to ER-negative breast tumours of which 26.2% were c-erbB2-positive (p<0.0001); 10.9% of PR-positive tumours were c-erbB2-positive whereas 25.3% of PR-negative tumours were c-erbB2-positive (p<0.0001). In the case of invasive lobular carcinoma there was no similar correlation due to either small patient numbers or a lack of correlation. For the correlation of ER and c-erbB2, the OR was 0.36, 95% CI: 0.09-1.38; p=0.14. For the PR and c-erbB2 correlation, the OR was=0.35 (95% CI 0.11-1.14; p=0.08). In ER-positive lobular carcinoma, 3.5% of cases were c-erbB2-positive (in PR-positive cases, it was 3.1%), whereas in ER-negative invasive lobular carcinoma this percentage was 9.1% (in PR-negative cases it was 8.2%).

Local recurrences and histological subtypes (Table IV). Distant metastases were found less frequently than local recurrence (5.6% *vs*. 16.5%) without regard to the histological subtype. The question of whether one of the main subtypes of invasive breast cancer tended to induce more local recurrence or distant metastasis was addressed only by the study of group A patients. A significantly lower frequency of local recurrences was observed in lobular carcinoma (3.6% *vs*. 6.1%; p=0.039). For distant metastasis, only a trend for decreased numbers of cases of distant metastasis in lobular carcinoma was observed (13.8% *vs*. 17.3%; p=0.07).

In patients below 60 years of age suffering from lobular carcinoma, the frequency of distant metastasis was 19.3% and in patients above 60 years of age it was 9.1% (p=0.002). In ductal carcinoma, the data were similar, with 17.0% distant metastasis for patients below the age of 60 years and 10.3% for those above the age of 60 years (p=0.002). Therefore younger age favoured distant metastasis in both subgroups. The frequency of a local recurrence in invasive ductal carcinoma was 5.2% for patients below 60 years of age and 3.6% for patients above 60 years of age (p=0.23). Local recurrences in invasive lobular carcinoma were observed in 2.8% of patients below 60 years of age and 1.3% in patients above 60 years of age (p=0.50).

Age and histological subtypes. The average age and the histological subtype of invasive breast cancer were correlated. Invasive lobular carcinoma patients had an average age of 60.95 years (SD=12.32 years, range: 26-101 years) compared with invasive ductal carcinoma patients who had an average age of 59.55 years (SD=13.34 years, range: 18-101 years; p<0.0001). When considering patient age and tumour histological type in a Cox regression model as independent prognosis factors, only age, but not the histological type, was found to be of independent prognostic value (age, p<0.0001; age×histological type, p=0.74; histological type, p=0.89)

Univariable survival analysis. The histological classification as either invasive ductal or lobular did not predict OS (p=0.75) or event-free survival (EFS; p=0.8 in group A patients) (Figure 2). ER status was not related to OS in lobular carcinoma (p=0.73), but was related to OS in ductal carcinoma (p<0.0001) (Figure 3) without concerning. However, this observation depended on the grading and was only true for G1 and G2 lobular carcinomas (p=0.56 and 0.13 respectively) and for G1 ductal carcinoma (p=0.16). ER status predicted disease outcome in G2 and G3 ductal carcinomas and G3 lobular carcinoma (p=0.0006, 0.007 and 0.002, respectively).

Table V. *Cox multivariable analysis for primary breast cancer.*

Variable	Cox coefficient	HR	SD	z-Score	*p*-Value	95% CI
ER^+ *vs*. ER^-	–0.29	0.75	0.05	–5.26	10^{-7}	0.67-0.83
PR^+ *vs*. PR^-	–0.20	0.81	0.05	–4.10	$5*10^{-5}$	0.73-0.89
Grade 2 *vs*. 1	0.22	1.24	0.10	2.24	0.025	1.03-1.50
Grade 3 *vs*. 1	0.55	1.73	0.10	5.41	10^{-8}	1.42-2.11
pN 1 *vs*. 0	0.69	2.01	0.05	15.08	10^{-15}	1.84-2.20
pN 2 *vs*. 0	1.32	3.73	0.07	18.52	10^{-15}	3.24-4.29
pN 3 *vs*. 0	1.33	3.78	0.16	8.40	10^{-15}	2.77-5.15
pT 2 *vs*. 1	0.46	1.59	0.05	9.16	10^{-15}	1.43-1.75
pT 3 *vs*. 1	0.74	2.10	0.08	9.34	10^{-15}	1.80-2.46
pT 4 *vs*. 1	1.06	2.91	0.07	15.33	10^{-15}	2.50-3.30
Age >60 *vs*. <60 years	0.63	1.87	0.05	14.85	10^{-15}	1.72-2.03
Lobular *vs*. ductal	–0.07	0.92	0.14	–0.50	0.58	0.72-1.21
ER×Histology	0.27	1.317	0.18	1.762	0.09	0.97-1.79
PR×Histology	–0.18	0.835	0.16	–0.762	0.21	0.64-1.09

SD, Standard deviation of Cox coefficient; HR, hazard ratio; 95% CI, 95% confidence interval for hazard ratio.

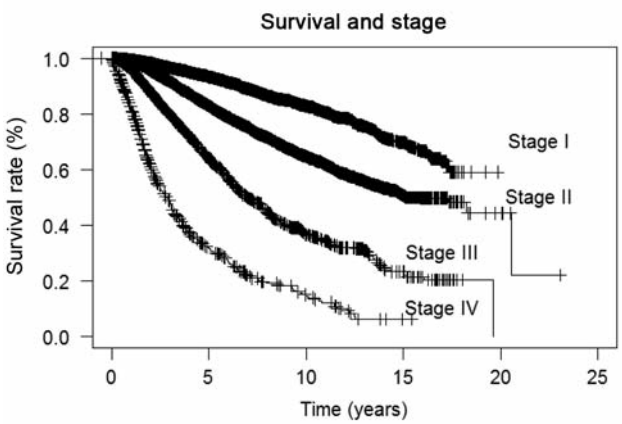

Figure 1. *Overall survival rate according to tumour stage.*

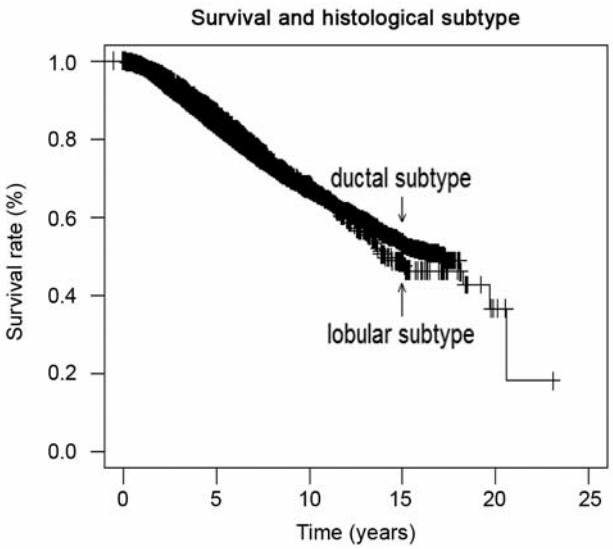

Figure 2. *Overall survival rate according to histological subtype.*

Multivariable survival analysis. The results of the Cox regression analysis are reported in Table V. PN, pT, tumour grade and age were strong predictors of poor disease outcome. The expression of ER and PR were predictors of survival. The histological subtype of invasive breast cancer did not predict disease outcome. There was no significant difference found when comparing a Cox model with ER, PR, grade, pN, pT and age with a model including the histological classification (p=0.463). For the cases of group A, the c-erbB2 score was available for 1,303 patients. A strong membranous expression of c-erbB2 (score 3) in group A was not a multivariable predictor of poor disease outcome (z=0.56, p=0.580). There was no interaction found between the histological classification and c-erbB2 ER or PR expression.

Subgroup analysis. In the pT1 pN0 subgroup of invasive breast cancer, neither the expression of ER (z=0.07, p=0.94) and PR (z=–1.72, p=0.09) nor histology (z=–1.21, p=0.13) were predictors of good disease outcome . In pT4 invasive breast cancer, only the presence of PR (but not of ER or the histological subtype) was a predictor of a somewhat better disease outcome (ER: z=0.11, p=0.91; PR: z=–3.73, p=0.002; histology z=0.24, p=0.81). In patients aged under 40 years or over 80 years, neither the presence of ER (p=0.22, 0.15) or PR (p=0.20, 0.95) nor the histology (p=0.35, 0.35) were predictors of disease outcome.

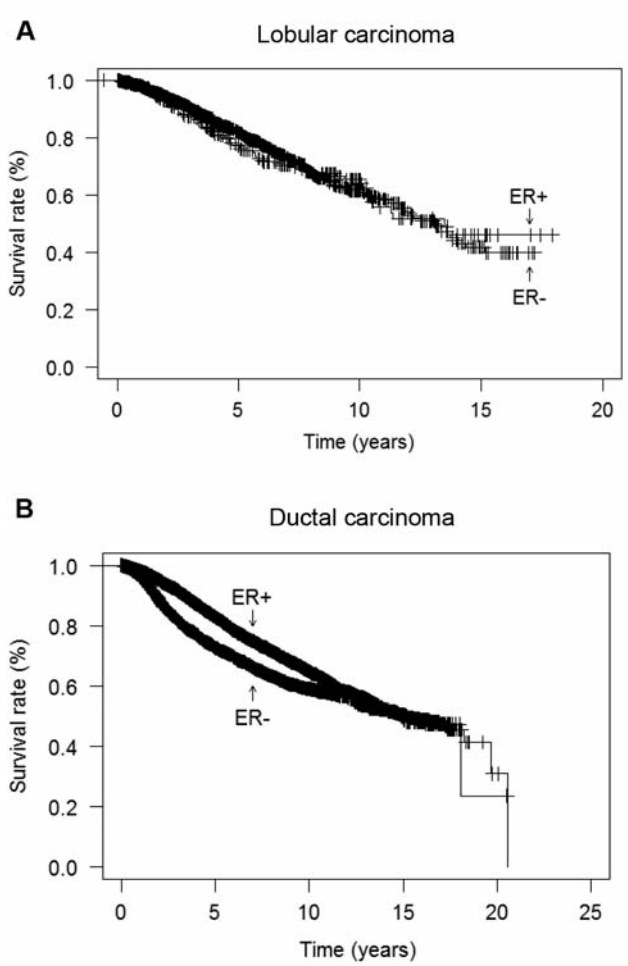

Figure 3. *Differences in overall survival according to ER and histological subtype. A: Lobular carcinoma and B: ductal carcinoma.*

Discussion

An increasing number of publications claim to identify either univariable or multivariable predictors of disease outcome or treatment response in invasive breast cancer. If the reporting system for breast cancer is performed as proposed by the TNM classification (2), the WHO proposal (1), the recommendations of the national consensus meetings of the American Society of Pathology (10) and the S3 Richtlinien Deutscher Gesellschaft für Pathologie (11), then an inordinate number of different types of invasive breast cancer can be discriminated to include T(1, 2, 3, 4), N(0, 1, 2, 3), G(1, 2, 3), M(0, 1), L(0, 1), V(0, 1), ER(0, 1), PR(0, 1), c-erbB2 (0, 1, 2, 3 or 0.1), histological subtypes (invasive ductal, invasive lobular or up to 30 specified subtypes) and R(0, 1, 2). As each of these parameters can be combined with each other, the number of possible types of breast cancer range from 6,144 (when only the basic variables are taken into consideration) to 1,658,880 different subtypes of invasive breast cancer (when the different histological subtypes, the menopausal status and the R status are taken into consideration). Each of these subtypes is a possible candidate for different treatment decisions. The rapidly increasing knowledge about the aetiology and tumour progression makes it inevitable to seek to rank the variables given above. Decision making in the treatment of breast cancer patients has to take into consideration, beside other variables such as research progress and findings, the results of retrospective breast cancer data banks as provided *e.g.* by Henson *et al.* (12-14). One strategy to overcome the problem of increasing numbers of invasive breast cancer subtypes is to give different clinical impacts to different variables by performing Cox regression analysis including all the well-known variables. Using three independent samples of invasive breast cancer (all from one region of Germany), the present study found that the disease outcome of invasive carcinoma is independent of the histological subtype when they are classified as either invasive ductal or lobular (Figures 2 and 3). Invasive carcinomas classified as specified were excluded from these analyses. Reporting invasive breast cancer as either ductal or lobular is recommended in all consensus papers (1, 2, 10, 11) published to date. In addition, an increasing number of published studies describe methods on how to discriminate between lobular and ductal invasive carcinoma with immunohistochemical methods (*e.g.* staining for β-catenin or E-cadherin (14)). Investigations concerning the clinical impact of this discrimination are conflicting (16-29).

Some authors claim that invasive lobular carcinoma is correlated to a better OS in patients overall (15, 16, 19, 25) than invasive ductal carcinoma breast cancer. Li *et al.* (25) observed a better disease outcome only in patients aged between 50 and 70 years. Subtyping of invasive lobular carcinoma as either diffuse (solid), mixed, classical, tubulo-lobular and alveolar, as proposed by Du Toit *et al.* (21), was not considered in the present study as no such subtyping was performed in the data and neither reproducibility nor multivariable clinical significance has been definitely proven for this subtyping (3) to date. Contrary to the above mentioned studies, the present study and some previous studies argued against the clinical impact of subtyping an invasive breast cancer as either ductal or lobular, regarding OS and EFS (19, 22, 23, 29). The present study argues clearly in favour of the null hypothesis that invasive ductal and lobular breast carcinomas do not differ with respect to disease outcome (Table II and Figure 2).

Nevertheless, the study revealed some clear-cut highly significant intrinsic relations between clinical or morphological features of breast cancer and histological subtyping. Specifically: (i) patients with lobular cancer tended to be older than those suffering from invasive ductal carcinoma, (ii) lobular carcinoma was more often ER- and PR-positive than ductal

carcinoma (Table III), and (iii) ductal carcinoma tended to be more often positive for c-erbB2 than lobular carcinoma. Therefore, these data suggest that invasive ductal and lobular breast carcinomas are biological subtypes without clinical impact on disease outcome.

The third hypothesis investigated in the present study was that invasive lobular carcinoma more frequently results in local recurrence than invasive ductal carcinoma. This hypothesis was considered because invasive lobular carcinoma grows diffusely and tends to be more often multifocal or multicentric. In the one group with useful data for testing this hypothesis (group A), there was no evidence found for confirming this hypothesis. In contrast, the data of group A showed that is more frequent in ductal carcinoma local recurrence than in lobular carcinoma (p=0.03).

The present study argued that lobular carcinoma is a biological entity without clinical impact. This is in line with a biomolecular study of 84 genes discriminating between lobular and ductal carinoma such as E-cadherin, or genes involved in the TFG-beta or Wnt signalling pathway (31). Similar results, using a different set of genes were published by Zhao *et al*. (32). Response to primary chemotherapy of anthracycline and, in some cases, taxane seems to be better in lobular than in ductal carcinoma as shown by Cristofanilli *et al*. (26). Jirström *et al*. (33) claimed that response to tamoxifen is less successful in ER-positive invasive lobular breast cancer than in ER-positive ductal breast cancer. In the present study, there were no tendencies found regarding the influence of the histological subtype on treatment response in the three treatment subsets available in the study, namely CMF-treated, anthracylince-treated and tamoxifen-treated subsets. In a recent study, Jaremko *et al*. (34) were able to find a correlation between a DNA polymorphism for a DNA repair enzyme (*XRCC1*) and treatment success of either anthracyline or cyclophosphamide/methotrexate/5-fluorouracil, but not for the histological subtype.

The present study had several shortcomings. Since the study considered only retrospective data, it was not possible to investigate all treatment modalities because of lack of data. For example, patients with trastuzumab treatment were not significantly represented in the present study and, therefore, an analysis of trastuzumab treatment was not performed, as it would not have been statistically valid. A second disadvantage of a retrospective study is the high number of pathologists giving the final diagnosis, preventing high reproducibility of morphological classifications. However, these disadvantages do not exclude the use of retrospective data analysis for gaining information about the clinical impact of a given variable.

In conclusion, there was no evidence found, either univariable or multivariable, arguing in favour of the hypothesis that the histological subtype (excluding specified types) predicts disease outcome (OS and EFS for group A). The data of the present study, however, were consistent with the hypothesis that invasive ductal and lobular carcinomas are different biological entities differing in some characteristics such as high frequency of ER and PR and low frequency of c-erbB2 positivity. In multivariable Cox regression analysis T, N, grading, ER, PR and age were found to predict prognosis of invasive breast cancer.

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